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Determinants of oral cavity cancer recurrence in Pakistan: findings from a cross-sectional study using an institutional cancer registry

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Abstract

Introduction Pakistan has a high prevalence of oral cavity cancer (OCC) with a significant recurrence rate. This study aims to explore the factors associated with OCC recurrence in Karachi, Pakistan.

Methods This cross-sectional study was conducted at the Aga Khan University Hospital (AKUH) Karachi, Pakistan, using data from the AKUH Cancer Registry. A total of 1692 biopsy-confirmed cases of OCC including cancers of mucosal lip, tongue, gum, oral cavity floor, palate and other subsites like retromolar area, diagnosed between May 2011 and December 2020, were included in our study.

Results Of the 1692 patients, 611 (36.1%) experienced recurrence. Being male was associated with significantly increased odds of OCC recurrence compared to being female (Prevalence Odds Ratio (POR) = 1.70, 95% CI = 1.25–2.30). Moderately and poorly differentiated tumors had higher odds of recurrence (POR = 1.44, 95% CI = 1.02–2.02 and POR = 2.35, 95% CI = 1.49–3.71 respectively). Lymph node involvement was significantly associated with increased odds of recurrence. Patients with N1, N2 and N3 lymph node involvement had significantly higher odds of recurrence (POR = 1.45, 95% CI = 1.02–2.07 for N1, POR = 2.12, 95% CI = 1.57–2.87 for N2 and POR = 3.50, 95% CI = 1.72–7.11 for N3 respectively). Surgical treatment outside AKUH was associated with higher OCC recurrence (POR = 1.68, 95% CI = 1.12–2.50). Surgery alone (POR = 0.02, 95% CI = 0.00-0.16) and in combination with radiation (POR = 0.02, 95% CI = 0.00-0.16) or chemoradiation (POR = 0.04, 95% CI = 0.01–0.33) was protective against recurrence.

Conclusion This study's findings identified factors increasing oral cavity cancer recurrence, highlighting the importance of considering these factors in the management and follow up of patients with OCC. Understanding these factors will not only help enhance patient care, but also improve patient education about their disease prognosis. Further research is needed to explore the underlying mechanisms and develop targeted interventions to improve outcomes for patients with OCC.

Keywords Oral cavity cancer, Pakistan, Recurrence, Grade, Lymph node

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Introduction

Oral cavity cancer (OCC) is a malignancy that forms in the tissues of the mouth such as mucosal lip, tongue, gum, oral cavity floor, and palate. It can be broadly classified as squamous cell carcinoma (most common) and non-squamous cell carcinoma, which includes mucoepidermoid carcinoma, adenocarcinoma and adenoid cystic carcinoma [1]. OCC continues to be a worldwide public health concern, with up to 1.0-fold rise in incidence and mortality globally alongside highest age-standardized rates of incidence and mortality in Pakistan from 1990 to 2017 [2]. Australia has reported an almost 4.5-fold increase in diagnoses and a 19-fold increase in deaths in the last 36 years [3]. A systematic review conducted in Iran revealed an Age-Standardized Incidence Rate (ASIR) of 1.96 per 100,000 for men and 1.36 per 100,000 for women [4]. Similarly, a World Health Organization report showed that while male mortality from OCC had declined in places such as Argentina, Australia and Hong Kong, it has been on the rise in some European countries and the United Kingdom [5]. While radical surgery in combination with radiotherapy has effectively reduced the rate of local recurrence in OCC, the mortality remains high, with poor overall survival [6].

In terms of the risk factors, alcohol, different forms of smokeless tobacco including betel nut, human papilloma virus, and active and passive smoking have consistently shown a strong relation with oral cancer across the literature [7]. Moreover, various genetic changes have also been linked with the development of oral cancer [8], with chronic inflammation and precancerous lesions also being implicated as pathogenic factors [9]. Mutations in signaling pathways such as WNT, MAPK and PI3K have also been explored as molecular mechanisms [10].

The standard of care for patients with OCC following curative therapy involves routine follow-up due to the elevated risk of secondary primary tumors and recurrent disease. Recurrence of OCC is an important prognostic factor for survival. It can either be loco-regional or distant [11]. Recurrence is associated with a grim prognosis which may be attributable to tumors unamenable to salvage surgery, and development of resistance to chemotherapeutic agents which are considered the modality of choice for management of advanced or recurrent disease [12]. Additionally, most of the patients are unable to afford state of the art targeted treatments or immune checkpoint inhibitors with no access to clinical trials in low- and middle-income countries (LMIC); hence, limiting systemic options in recurrent or metastatic setting. Most oral cancer recurrences occur within the first 2 years following surgical treatment [13]. Therefore, it is crucial to enhance postoperative follow-up and promptly detect any recurrence. The risk of recurrence increases with time, with the 1-, 5- and 10-year rates of recurrence being 17%, 30% and 37% respectively [14].

A study done in Karachi, Pakistan showed that a tumor size of T4, surgery and adjuvant therapy, a high cervical nodal disease burden, and margin involvement were associated with a higher risk of recurrence [15]. A similar study from the USA reported that high grade tumors or those with high nodal ratios had a higher recurrence rate [16]. Moreover, a report of 275 patients in China revealed T stage, degree of differentiation, and pN stage to be independent risk factors for relapse [17].

Limited data exists regarding oral cancer and its recurrence in Pakistan. As per a recent report in 2020, oral cancer ranks as the second most common and fatal cancer in the country, being the most common in males [18]. Given its high frequency, it is imperative to comprehend the underlying principles and roots of its recurrence. This study aims to explore a range of factors that could affect recurrence of OCC in Pakistani population, with a comprehensive investigation of sociodemographic and clinicopathological characteristics.

Materials and methods

This cross-sectional study was conducted at the Aga Khan University Hospital, Karachi, Pakistan and involved retrospective analysis of data obtained from the hospital's cancer registry. Patients diagnosed with OCC between May 2011 and December 2019 from our cancer registry were included in the analysis. All cases were confirmed through retrieval of histopathologic records and the date of reporting of the biopsy was considered the date of diagnosis.

All variables including age, gender, history of tobacco/alcohol use, tumor characteristics, clinical and pathological staging (according to the American Joint Committee on Cancer [AJCC] 7th and 8th editions) and vital status were abstracted. For cases diagnosed before 2017, the AJCC 7th edition was used which was transitioned to the AJCC 8th edition in 2018 to align with updated staging criteria and international standards. ICD-9 codes were used for all cases diagnosed in the year 2020 and earlier. For cases diagnosed after 2020, ICD-10 codes were used, based on the coding available in the charts at the time of abstraction by the Indexing and Coding Unit.

The treatments received including surgery alone or in combination with radiation or chemoradiation, chemoradiation alone, palliative care and others were also abstracted and vital status was further updated during the period from May 2, 2023, to August 1, 2023. Any entries with incomplete information were excluded from the analysis.

Categorical data was summarized using frequencies and percentages. The dependent variable was recurrence (Yes/No). Univariate analysis was done using simple

logistic regression and results are reported as crude PORs and 95% confidence intervals. Multivariable analysis was performed using a multiple logistic regression to calculate adjusted PORs and 95% confidence intervals. A stepwise approach was used with both forward selection and backward elimination methods to obtain the final multivariable model. A p value of less than 0.05 was considered significant. Statistical Package for Social Sciences software version 21 was used for the statistical analysis. Ethical approval for this study was obtained from the Ethical Review Committee (ERC) of The Aga Khan University.

Results

We identified a total of 2238 cases of OCC out of which 546 were removed due to incomplete information. Table 1 presents the distribution of sociodemographic, personal, clinical, and pathological factors and results of univariate analysis for associations with recurrence. 41.2% of recurrent OCC patients were less than 35 years old, 36.5% were 35 to 50 years old, and 34.2% were older than 50 years. The rate of recurrence was higher in males (38.4%) than in females (28.7%) ($p < 0.001$). Patients who had poorly differentiated cancer faced more recurrences (51.6%) ($p < 0.001$). However, there were no differences in recurrence rate when it came to age, tumor site, and histopathology. A significant association was observed between patients who had a family history of cancers other than head and neck region and recurrence ($p = 0.026$). Moreover, tumor grade and TNM staging were significantly associated with recurrence ($p < 0.001$). AJCC stage 4 cancers were the highest in number, with recurrence in 339 (46.1%) and no recurrence in 396 (53.9%) ($p < 0.001$). 129 (70.9%) patients who had recurrence died, while 482 (31.9%) of recurrent OCC patients were alive ($p < 0.001$). 339 (46.1%) patients who had recurrence also had metastasis ($p < 0.001$). Surgery outside of AKUH had higher likelihood of recurrence as 100 (55.2%) patients faced recurrence ($p < 0.001$). The highest number of patients were given surgery in combination with chemoradiation in terms of overall treatment modality with 397 (45.3%) facing recurrence while 480 (54.7%) did not have recurrence. Patients who were given palliative care, chemotherapy only or other forms of treatment had the highest recurrences (64.4%) ($p < 0.001$).

In the univariate analysis of sociodemographic characteristics, the variables found to be associated with OCC recurrence included male gender, family history of cancers other than OCC, and occupation. Males had a higher recurrence than females (POR = 1.55, 95% CI = 1.21–1.98). Similarly, those with a family history of any cancer were at higher odds for recurrence (POR = 1.68, 95% CI = 1.06–2.65). However, there was no significant association between a family history of OCC and recurrence (POR = 0.93, 95% CI = 0.60–1.42).

For the clinicopathological characteristics of our patients, univariate analysis showed significant associations of OCC recurrence with moderate and poor tumor grade, stage 4, tumor sizes T3 and T4, lymph nodes N1 to N3 and metastasis. With reference to well differentiated tumors, both moderately differentiated (POR = 2.14, 95% CI = 1.62–2.82) and poorly differentiated (POR = 4.00, 95% CI = 2.74–5.83) tumors demonstrated elevated odds of recurrence, with the latter having a stronger association. For the AJCC classification, only stage 4 tumors had a significant association with recurrence (POR = 2.45, 95% CI = 1.79–3.36). Compared to T1, both T3 and T4 tumors had increased odds for recurrence (POR = 1.58, 95% CI = 1.13–2.21 and POR = 1.89, 95% CI = 1.39–2.57 respectively). There was also an increase in recurrence with increasing nodal burden relative to N0 (POR = 1.96, 95% CI = 1.43–2.70 for N1, POR = 3.28, 95% CI = 2.54–4.25 for N2 and POR = 6.28, 95% CI = 3.25–12.15 for N3). Distant metastases were also significantly related with increased recurrence (POR = 2.26, 95% CI = 1.84–2.77). Surgery alone (POR = 0.14, 95% CI = 0.08–0.23) and in combination with radiation (POR = 0.17, 95% CI = 0.10–0.29) or chemoradiation (POR = 0.46, 95% CI = 0.29–0.72) was protective against recurrence with reference to palliative care, chemoradiation only or other modalities of treatment. Surgery done outside AKUH was associated with higher odds of recurrence (POR = 2.49, 95% CI = 1.82–3.40).

In the multivariable model (Table 2), after adjusting for significant variables identified in univariate analysis, male gender had higher odds of recurrence compared to females (adjusted POR = 1.70, 95% CI = 1.25–2.30). Both moderately differentiated and poorly differentiated tumors posed greater odds of recurrence (adjusted POR = 1.44, 95% CI = 1.02–2.02 and adjusted POR = 2.35, 95% CI = 1.49–3.71 respectively) compared to well differentiated tumors. Lymph node stages N1, N2 and N3 demonstrated increased odds of recurrence (adjusted POR = 1.45, 95% CI = 1.02–2.07, adjusted POR = 2.13, 95% CI = 1.56–2.91 and adjusted POR = 3.44, 95% CI = 1.67–7.09 respectively) with higher nodal staging having a stronger association. Surgical resection done outside AKUH proved to be another important factor associated with recurrence (adjusted POR = 2.49, 95% CI = 1.82–3.40) compared to surgical resections done at AKUH. Surgery alone (adjusted POR = 0.02, 95% CI = 0.00-0.16) or in combination with radiation (adjusted POR = 0.02, 95% CI = 0.00-0.16) or chemoradiation (adjusted POR = 0.04, 95% CI = 0.01–0.33) was also protective against recurrence with reference to palliative, chemoradiation alone or other modalities of treatment.

Table 1 Distribution and univariate analysis of sociodemographic, personal, clinical, and pathological factors associated with oral cavity cancer recurrence in AKUH, Karachi, Pakistan ($n = 1692$)

Characteristics	Recurrence	No recurrence	*p value	Crude POR [95% CI]
	n (%)	n (%)		
Age			0.161	
< 35	91 (41.2)	130 (58.8)		0.74 [0.55–1.01]
35–50	265 (36.5)	461 (63.5)		0.82 [0.60–1.12]
> 50	255 (34.2)	490 (65.8)		ref
Gender			**< 0.001**	
Male	498 (38.4)	800 (61.6)		1.55 [1.21–1.98]
Female	113 (28.7)	281 (71.3)		ref
Marital status			0.483	
Married	574 (36.3)	1006 (63.7)		1.13 [0.75–1.69]
Single/Widowed	37 (33.6)	73 (66.4)		ref
Past history of alcohol use			0.553	
Yes	31 (39.2)	48 (60.8)		1.15 [0.72–1.83]
No	580 (35.6)	1033 (64.0)		ref
Past history of tobacco use			0.965	
Yes	446 (36.1)	788 (63.9)		1.01 [0.80–1.26]
No	165 (36.0)	293 (64.0)		ref
Family history of head and neck cancer			0.738	
Yes	35 (34.7)	66 (65.3)		0.93 [0.60–1.42]
No	541 (36.3)	949 (63.7)		ref
Family history of any other cancer			**0.026**	
Yes	37 (48.1)	40 (51.9)		1.68 [1.06–2.65]
No	574 (35.5)	1041 (64.5)		ref
Payment mode			0.239	
Out of pocket	568 (35.7)	1022 (64.3)		0.78 [0.51–1.18]
Insurance/Panel/Welfare/Others	40 (41.7)	56 (58.3)		ref
Primary tumor site			0.177	
Lip	13 (23.6)	42 (76.4)		0.68 [0.26–1.80]
Tongue	146 (33.8)	286 (66.2)		1.12 [0.52–2.43]
Gum, floor of mouth and palate	99 (37.4)	166 (62.6)		1.31 [0.60–2.89]
Buccal mucosa	343 (37.8)	565 (62.2)		1.34 [0.63–2.85]
Others like retromolar area	10 (31.3)	22 (68.8)		ref
Histopathology			0.537	
Squamous cell carcinoma (keratinizing)	321 (36.4)	562 (63.6)		0.92 [0.46–1.87]
Squamous cell carcinoma (non-keratinizing)	4 (66.7)	2 (33.3)		3.23 [0.52–20.20]
Squamous cell carcinoma (spindle cell)	7 (43.8)	9 (56.3)		1.26 [0.38–4.20]
Squamous cell carcinoma (not otherwise specified)	266 (35.3)	487 (64.7)		0.88 [0.44–1.79]
Others**	13 (38.2)	21 (61.8)		ref
Tumor grade			**< 0.001**	
Poorly differentiated	95 (51.6)	89 (48.4)		4.00 [2.74–5.83]
Moderately differentiated	361 (36.4)	632 (63.6)		2.14 [1.62–2.82]
Well differentiated	82 (21.1)	307 (78.9)		ref
AJCC stage			**< 0.001**	
4	339 (46.1)	396 (53.9)		2.45 [1.79–3.36]
3	89 (28.7)	221 (71.3)		1.15 [0.79–1.67]
2	72 (22.1)	254 (77.9)		0.81 [0.55–1.19]
0,1	66 (25.9)	189 (74.1)		ref
T stage			**< 0.001**	
4	197 (43.0)	261 (57.0)		1.89 [1.39–2.57]
3	120 (38.7)	190 (61.3)		1.58 [1.13–2.21]
2	161 (29.4)	387 (70.6)		1.04 [0.77–1.42]
1	89 (28.5)	223 (71.5)		ref

Table 1 (continued)

Characteristics	Recurrence	No recurrence	*p value	Crude POR [95% CI]
Nodal stage			**< 0.001**	
3	29 (67.4)	14 (32.6)		6.28 [3.25–12.15]
2	209 (52.0)	193 (48.0)		3.28 [2.54–4.25]
1	86 (39.3)	133 (60.7)		1.96 [1.43–2.70]
1	184 (24.8)	558 (75.2)		ref
Metastasis			**< 0.001**	
Yes	339 (46.1)	396 (53.9)		2.26 [1.84–3.40]
No	259 (27.5)	684 (72.5)		ref
Surgery done at hospital			**< 0.001**	
Outside AKUH	100 (55.2)	81 (44.8)		2.49 [1.82–3.40]
AKUH	481 (33.2)	969 (66.8)		ref
Overall treatment modality			**< 0.001**	
Surgery only	89 (20.0)	356 (80.0)		0.14 [0.08–0.23]
Surgery + Radiation	67 (23.9)	213 (76.1)		0.17 [0.10–0.29]
Surgery + Chemoradiation	397 (45.3)	480 (54.7)		0.46 [0.29–0.72]
Palliative/Chemoradiation only/Others	58 (64.4)	32 (35.6)		ref

Abbreviations: AJCC-American Joint Committee on Cancer, AKUH-Aga Khan University Hospital, *p value for chi square, POR: prevalence odds ratio, CI: confidence interval, OCC: Oral Cavity Cancer, NOS: Not otherwise specified, **Others include rarer morphologic subtypes of squamous cell carcinoma such as verrucous carcinoma, adenosquamous carcinoma

Table 2 Multivariable analysis of characteristics associated with oral cavity cancer (OCC) recurrence in AKUH, Karachi, Pakistan

Characteristics	*Adjusted POR [95% CI]
Gender	
Male	1.70 [1.25–2.30]
Female	ref
Grade	
Poorly differentiated	2.35 [1.49–3.71]
Moderately differentiated	1.44 [1.02–2.02]
Well differentiated	ref
Nodes	
N3	3.50 [1.72–7.11]
N2	2.12 [1.57–2.87]
N1	1.45 [1.02–2.07]
N0	ref
Surgery done in hospital	
Outside AKUH	1.68 [1.12–2.52]
AKUH	ref
Overall treatment modality	
Surgery	0.02 [< 0.01–0.16]
Surgery + Radiation	0.02 [< 0.01–0.16]
Surgery + Chemoradiation	0.04 [0.01–0.33]
Palliative/Chemoradiation only/Others	ref

*Multivariable Analysis using logistic regression, adjusted for gender, tumor grades, nodes staging, surgery done in hospital and treatment modalities,

Discussion

Male gender, poorly differentiated tumor grade, lymph node involvement, and the hospital where surgery was performed were significant factors associated with OCC recurrence in our population. Our study demonstrated a protective effect of surgery alone or in combination with other treatment modalities such as radiation or chemoradiation against relapse. With regards to the epidemiology of tumor sites, our observations are consistent with previous literature showing that tongue and buccal mucosa are the most frequently reported tumor sites [19, 20]. Another study from Karachi observed the highest percentages of tumor sites were the buccal mucosa (56.0%) and tongue (21.0%) which is similar to our study results [21]. The prevalence of buccal mucosa could be attributed to the frequent consumption of gutka (smokeless tobacco) in Pakistani population which is placed in the buccogingival sulcus [22]. Despite the recent rise in tobacco prices, consumption continues to increase, even among low-income groups with limited resources [23]. Our study results of prevalent tumor sites are similar to a study by Wang et al. that reported greater involvement of buccal and tongue cancer with higher recurrence [24]. Although their study linked tumor site to recurrence, we did not observe this relationship in our analysis. The lack of this finding has been corroborated by some other studies as well [17, 19].

High OCC recurrence represents a significant public health challenge in Pakistan. A study conducted at Patel Hospital reported a recurrence rate of 37% among 450 patients [25]. At Liaquat National Hospital in Karachi, recurrence rates have been reported as 30% among buccal cancer cases in one study and 58% among OCC cases in another study [26, 27]. Similarly, another study from our country observed recurrence in 31% of the OCC cases [28].

Our findings are consistent with previous studies indicating male gender association with recurrence as reported by a study done on Mongolian population where men were found to have a 3.8 times higher risk of relapse [19]. The higher recurrence could be explained by

the increased incidence of OCC and tobacco use among males [29].

Recurrence is more likely to occur in tumors that are poorly differentiated or have a high nodal ratio. Poorly differentiated tumors have not only been shown to be related to recurrence, but are also candidates for suboptimal outcomes, a factor possibly influenced by the genetic makeup of the tumor itself [16, 30, 31]. Another retrospective review from Taiwan is consistent with our findings by concluding higher grades as an adverse factor of prognosis and recurrence [32]. A 19-year review of hospital records in Seoul and a 5-year records review from Spain also showed the relation of poor grading with recurrence [33, 34].

Our study findings are consistent with numerous previous studies that have found lymph node involvement to be a significant risk factor for recurrence [16, 19, 35–38]. A considerable number of features could influence this effect, including but not limited to laterality, number, size, anatomical level of involvement and extracapsular spread [39]. Smokeless tobacco can be attributed as the cause in most of our cases, as hypoxic mucosa induces distinct molecular/chromosomal changes leading to resistant tumors, hence likely early recurrences [40]. It is also confirmed that OCC patients with lymph nodes recurrence have poor outcomes [41]. Another study conducted at our institution reported lymph node ratio as a significant prognostic marker for tongue cancer [42].

Our study found that most OCC cases treated at AKUH with a high-quality multidisciplinary approach and treatment modalities were protected against recurrence. Consistent with our study findings, a comprehensive 14-year review conducted at another hospital in Pakistan reported a disease-free survival (DFS) rate of 71% among patients treated with surgery, with or without adjuvant therapy [43]. Radical neck dissection and comprehensive treatment play a crucial role in reducing the burden of OCC recurrence [17].

Our study showed an important finding that surgery done outside AKUH was associated with higher odds of recurrence. It is crucial to highlight disparities in treatment, particularly the unavailability of frozen sections and comprehensive lymph node dissection in many cancer hospitals. Moreover, quality of radiation and sub-optimal chemotherapy doses for patients who opt for treatment at outside centers mostly due to financial limitations explain the higher recurrence of OCC in our population [44, 45]. In Pakistan, OCC is highest among males belonging to poor socioeconomic status, unable to afford optimal cancer treatment [23].

Our study was limited by the lack of information on potential factors for recurrence such as muscle invasion, peripheral neural invasion, and depth of invasion. Future research should focus on examining these factors to identify patients at high risk of recurrence and identify potential intervention strategies accordingly for reducing recurrence in OCC. Moreover, although the data is limited to a single center, AKUH is a tertiary care facility serving a diverse patient population across Pakistan, which enhances the generalizability of our findings. Despite inherent limitations in this registry-based analysis, our study benefits from the State-of-the-Art Cancer Registry at Aga Khan University, Karachi, which employs CNext software to ensure high-quality cancer data and minimize potential biases in retrospective studies [46]. AKUH maintains this cancer registry program, highlighting the importance of cancer data collection and analysis in Pakistan.

Conclusion

Male gender, poorly differentiated tumor grade and lymph node involvement were significant factors associated with OCC recurrence in our population. This study provides a baseline for future multicenter studies with inclusion of variables like muscle invasion, perineural invasion and depth of invasion. The identification of associated risk factors could guide towards risk stratification and targeting high risk population for better prognosis. Supportive evidence like this could also provide an incentive towards understanding the behaviour and recurrence mechanisms of poorly differentiated tumors.

Abbreviations

AKU	Aga Khan University
CI	Confidence interval
OR	Odds Ratio
OCC	Oral Cavity Cancer

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Author contributions

U.S. contributed in conceptualization, ethical approval, methodology, investigation, data curation, validation, statistical analysis, manuscript writing-editing & reviewing, project administration & supervision. H.J. and M.S.A. conducted the literature review, data curation, statistical analysis, manuscript writing. H.A.P. and Y.A.R. as subject experts contributed in manuscript writing-editing & reviewing. All authors discussed the results and provided feedback for the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Ethical Review Committee (ERC) of The Aga Khan University, Karachi, Pakistan (ERC AKU ID #8381). Since this study was based on data retrospectively obtained

from the cancer registry, informed consent was not required as all data was anonymized.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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